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RECENT WORK ON SYNTHETIC PHARMACEUTICALS DONE BY THE RUMANIAN CHEMICAL ENTERPRISES FOR RESEARCH AND SEMI-INDUSTRIAL PRODUCTION (ICEPS INSTITUTE)

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[A Digest]

Since its inception, ICEPS has played a dominant role in research and development in the field of synthetic pharmaceuticals introduced into production in Rumania. The author outlines briefly the difficulties which this institute has encountered in connection with its work on synthetic pharmaceuticals and medicinals. Any problems accepted by the institute must pass through the following four phases: (a) laboratory research; (b) planning and designing of pilot-plant installations; (c) construction of pilot-plant installations and experimentation in pilot-plant equipment accompanied, if necessary, by changes in the original installation; (d) final designing of the full-scale industrial installation.

As an example of the work done at ICEPS, the author mentions the fact that full-fledged production of sulfathiazol has been developed and illustrates his comments on the subject with a complete industrial flowsheet of that production. Other synthetic pharmaceuticals introduced into production by ICEPS comprise the sulfonamide, formothiazol; the antisyphilitics, trivarsol and pentarsol; the analgesics, antipyrine and pyramidon; and the antimalarial, paludrine. The synthesis of pharmacologically active compounds is naturally connected with other branches of the synthetic organic industry by reason of a common source of crude materials and common intermediates, so that work in the field of pharmaceuticals is conducted from that standpoint.

The author emphasizes the two newest products tackled by ICEPS, namely, nitrofurane (actually 5-nitro 2-furane aldehyde semicarbazone) and chloromycetin. As far as nitrofurane is concerned, a collaborator of the Institute

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has developed a new and very ingenious method for its synthesis suitable for application on a semi-industrial and industrial scale. As regards chloromycetin, little that is new could be contributed to its chemistry.

One of the syntheses of chloromycetin starts with p-nitrobenzaldehyde and involves the use of nitromethane. This method was discarded because of the explosive properties of nitromethane, which is applied here as the sodium salt derived from it.

The second method starts with p-nitrotoluene and has been found to yield satisfactory results on a laboratory scale as far as preparation of small quantities of chloromycetin for distribution to biological research workers is concerned. However, this synthesis involves a reaction of p-nitrobenzoic acid chloride with malonic acid ester (resulting in p-nitroacetophenone by the way of a malonic ester ketone synthesis after the acyl group has been introduced into the malonic acid ester molecule with the aid of magnesium), bromination of the methyl group of p-nitroacetophenone, and other steps which the Rumanian workers were unable to master from the technological point of view. In view of the difficulties encoutered in that respect, the following synthetic method was investigated: hippuric acid → hippuric acid chloride → introduction of the hippuric acid group into benzene by a Friedel-Crafts synthesis → condensation with formaldehyde → nitration.

This method led to satisfactory results on the laboratory scale, but some difficulties remain to be ironed out before it can be applied in full-scale industrial production. Attempts were made to substitute acetyl glycocoll or toluene sulfonamide N-acetic acid for hippuric acid in this synthesis and the results obtained were roughly the same as with hippuric acid.

Production of chloromycetin in quantity is being contemplated in Rumania. As far as production of this antibiotic by the fermentation method is concerned, the facilities of a streptomycin plant, construction on which was started in 1945 and completed in 1948, are being utilized.

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